Original Research Article

Raised serum uric acid levels as an independent risk factor for the development of hypertension

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Abstract

Background: Raised serum uric acid has been reported to be associated with an increased risk of coronary heart disease and is commonly encountered with essential hypertension, even untreated hypertension, and type 2 diabetes, which are in turn associated with coronary heart disease.
Aim: To estimate the levels of uric acid in patients with essential hypertension. To correlate the levels of uric acid with the severity of hypertension in newly detected hypertensive patients. To compare the levels of uric acid in hypertensives with that in non hypertensives so as to assess the role of uric acid as a risk factor for hypertension.
Materials and Methods: This study was an age and sex matched prospective case control study. Matching for other confounding factors such as diet, alcohol and smoking was also done. The study was conducted during the period from September 2010 to September 2012 after obtaining the clearance from the Institutional Ethics Committee. **Inclusion Criteria**: Patients of age > 18 years, newly detected patients of essential hypertension and patients with essential hypertension on treatment. **Exclusion Criteria**: Patients with renal failure. Patients on treatment with drugs altering uric acid levels such as thiazides, loop diuretics, pyrazinamide and allopurinol. Lymphoproliferative or myeloproliferative disorders. Secondary hypertension and pregnancy induced hypertension. The study included a total of 142 patients of which 80 were cases (hypertensives) and 62 were controls (non hypertensives).
Results: The range of the serum uric acid in cases was 1.40 to 11.30 mg/dl. In hypertensive males it was found to be from 1.40 to 11.30 mg/dl and in hypertensive females it was found to be from 2.70 to 11.10 mg/dl. The range of the serum uric acid in controls was 1.50 to 6.50 mg/dl. In hypertensive

males it was found to be from 1.50 to 6.50 mg/dl and in hypertensive females it was found to be from 1.60 to 6.20 mg/dl. Serum uric acid is significantly elevated in hypertensives as compared to normotensive individuals. Serum uric acid can be used probably as an early biochemical marker to determine the severity of hypertension as stage 2 hypertensives had more elevation in serum uric acid levels as compared to other hypertensives. The uric acid levels did not differ significantly between hypertensives with and without treatment. There is a considerable difference in the mean serum uric acid levels between stages 1, 2 and isolated systolic hypertension in the newly detected hypertensives but it is not of a linear correlation The total number of newly detected hypertensives were 39 out of which 13 were diagnosed as stage 1 hypertension, 22 as stage 2 hypertension and 4 as isolated systolic hypertension. The mean of the serum uric acid was 4.20 (1.37) mg/dl, 6.56 (1.40) mg/dl and 4.40 (1.40) in stage 1 hypertension, stage 2 hypertension and isolated systolic hypertension respectively, in newly diagnosed hypertensives.

Conclusion: Thus serum uric acid estimation can be used for aiding in the diagnosis of essential hypertension as well as in assessment of the severity.

Key words

Uric acid, Risk factor, Hypertension.

Introduction

Uric acid, which serves no biochemical function other than being an end product of purine metabolism, was first discovered in 1776. A Swedish chemist Scheele isolated it from a urinary tract stone. In 1797, a British chemist Wallaston detected uric acid in a tophus which was removed from his own ear. About 50 years later Alfred Baring Garrod, a British physician showed by chemical isolation that uric acid was abnormally high in gouty patients. In subsequent studies Garrod formulated a rational relationship between hyperuricemia and symptomatology of gouty patients. Association between hypertension and hyperuricemia was recognized when a family with a unique and unfortunate pedigree attended Hammersmith hospital in 1957. The father and six of the seven siblings had hyperuricemia, while the mother and all the siblings had hypertension [1]. This raised the question whether a raised serum uric acid was common in patients with hypertension. Raised serum uric acid has been reported to be associated with an increased risk of coronary heart disease and is commonly encountered with essential hypertension, even untreated hypertension, and type 2 diabetes, which are in turn associated with coronary heart disease. It is not known whether raised serum uric acid increases the risk of hypertension and type 2 diabetes independently of known risk factors such as age, obesity, alcohol consumption, and physical activity [2]. This study was done to determine whether raised serum uric acid levels were an independent risk factor for the development of hypertension.

Materials and methods

This study was an age and sex matched prospective case control study. Matching for other confounding factors such as diet, alcohol and smoking was also done. The study was conducted during the period from September 2010 to September 2012 after obtaining the clearance from the Institutional Ethics Committee.

Inclusion criteria: Patients of age > 18 years, newly detected patients of essential hypertension and patients with essential hypertension on treatment.

Exclusion criteria: Patients with renal failure. Patients on treatment with drugs altering uric acid levels such as thiazides, loop diuretics, pyrazinamide and allopurinol. Lymphoproliferative or myeloproliferative disorders. Secondary hypertension and pregnancy induced hypertension.

The study included a total of 142 patients of which 80 were cases (hypertensives) and 62 were controls (non hypertensives). Blood pressure has been recorded as the average of 2 or more readings at each of the 2 or more visits after initial screening. All the patients were subjected to relevant clinical examinations and laboratory investigations to look for secondary causes of hypertension. Essential hypertension is diagnosed in the absence of an identifiable cause. Hyperuricemia is defined as the serum uric acid >7.0 mg/dl in adult males, >6.0 mg/dl in adult females. Serum uric acid levels are best measured in the early morning venous blood sample after the patient is kept fasting for 12 hrs. Measurement of the serum uric acid was done by a chromatographic autoanalyser which absorbs light in the wavelength of 560 – 640 nm. Alternatively serum uric acid can be calculated as follows: The principle for the determination of Serum Uric Levels was devised by Trivedi and Kabasakalian with a modified Trinder peroxidase method using TBHB.

URIC ACID + O2 + H2O ------ Uricase---→ Allantoin + CO2 + H2O2

H2O2 + 4- AAP + TBHB ------Peroxidase--→ Quinoneimine + H2O

The intensity of chromogen (Quinoneimine) formed is proportional to the uric acid concentration in the sample when measured at 510 nm (510 -550nm). The patients were classified into the various stages of hypertension as per the JNC-7 mentioned in **Table – 1**.

Table – 1: shows criteria for classification of blood pressure.

Blood pressure staging	**Systolic blood pressure in mm of Hg**	**Diastolic blood pressure in mm of Hg**
Normal	<120	AND<80
Prehypertension	120-139	OR80-89
Stage 1 hypertension	140-159	OR90-99
Stage 2 hypertension	>160	OR>100
Isolated systolic hypertension	>140	AND<89

Table – 2: shows assay procedure.

Pipette into tubes marked	**Blank**	**Standard**	**Sample**
Working Reagent	1000 µl	1000 µl	1000 µl
Distilled Water	20 µl	-	-
Standard	-	20µl	-
Sample	-	-	20 µl

The active ingredient used in reagent I (Uric acid reagent) was 4-aminoantipyrine - 0.5 mmol/L, TBHB- 1.75 mmol/L, uricase (Bacillus species)- >120 U/L, peroxidase (Horseradish)- >500 U/L and tris buffer (ph 8.25 ± 0.1 at 20 C)-50 mmol/L. The active ingredient in uric acid standard used as reagent 2 was uric acid standard-6mg/dl. The Sample used was non haemolyzed serum or plasma separated from the cells as soon as possible. Recommended anticoagulants are heparin and EDTA. Uric acid is stable in serum or urine for 3 days at 20 - 25C (**Table – 2**).

Mix and incubate for 5 minutes at 37 C. Read the absorbance of standard and each sample at 510 nm (500 - 550 nm) or 510/630 nm on biochromatic analysers against reagent blank.

Calculations:

$$\text{Uric acid (mg/dl)} = \frac{\text{Absorbance of sample}}{\text{Absorbance of standard}} \times \text{Concentration of standard (mg/dl)}$$

Linearity: Up to 25mg/dl (1.5 mmol/L), for higher values, it is recommended to dilute the samples with normal saline, and repeat the assay, multiply the results with dilution factor. The color developed is stable for 15 minutes. The reagent and sample volume may be altered proportionally to accommodate various analyzer requirements. Specimens with Uric acid concentration greater than 1.5 mmol/L should be diluted with saline and re assayed. Multiply results by dilution factor. S.I. unit conversion factor, mmol/L x 16.8 = mg/dl. The reference values for serum uric acid levels were in males; 3.4-7.0 mg/dl; in females; 2.4-6.0 mg/dl.

Results

A total of 142 patients were studied during the period of 2 years from September 2010 to September 2012. This included 80 cases (hypertensives) and 62 controls (non hypertensives). Out of the 80 cases (hypertensives) 58 were males and 22 were females. Out of the 62 controls (non hypertensives) 38 were males and 24 were females (**Figure – 1**). The range of the serum uric acid in cases was 1.40 to 11.30 mg/dl. In hypertensive males it was found to be from 1.40 to 11.30 mg/dl and in hypertensive females it was found to be from 2.70 to 11.10 mg/dl. The range of the serum uric acid in controls was 1.50 to 6.50mg/dl. In hypertensive males it was found to be from 1.50 to 6.50 mg/dl and in hypertensive females it was found to be from 1.60 to 6.20 mg/dl. The mean serum uric acid in cases (hypertensives) was 5.32 mg/dl and controls (non hypertensives) was 3.75 mg /dl. The mean serum uric acid in male cases and controls was 5.49 mg/dl and 4.02 mg/dl respectively. The mean serum uric acid in female cases and controls was 4.86 mg/dl and 3.32 mg/dl respectively. Data analysis by T-test , done to compare the mean serum uric acid values in hypertensives with that of non hypertensives was proven to be significant with a p value of <0.001.

Figure – 1: shows sex distribution.

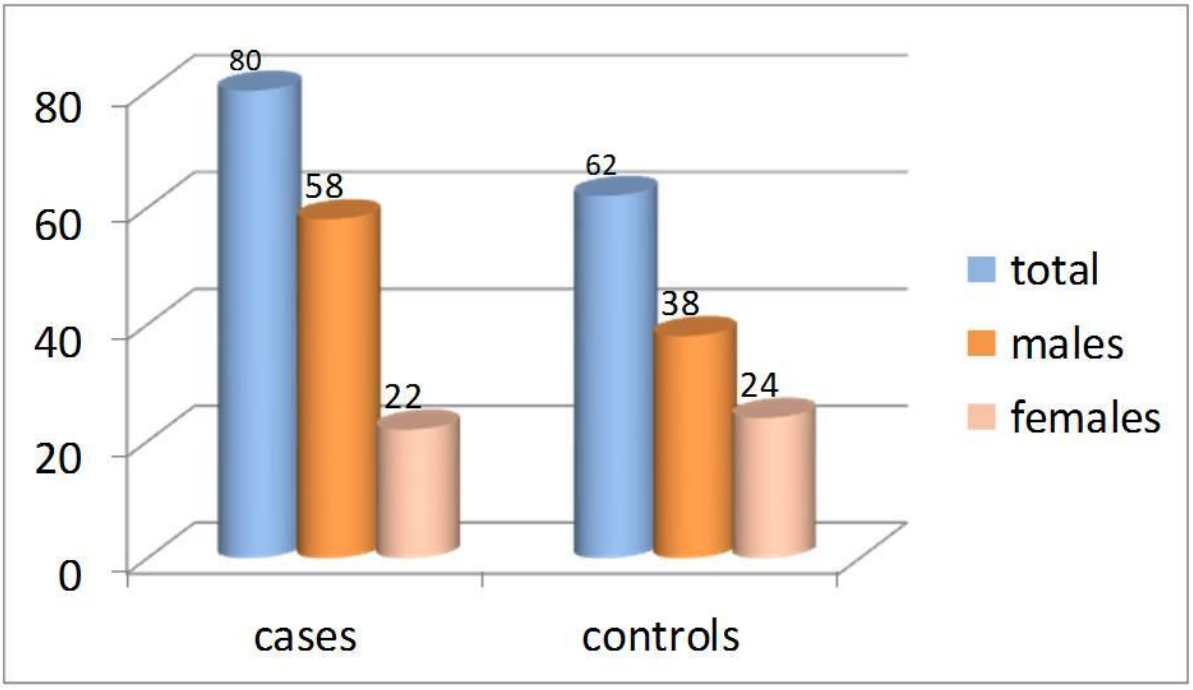


Table - 3 shows that out of the total 80 cases 14 were included under controlled hypertension, 26 under stage 1 hypertension, 31 under stage 2 hypertension and 9 under the isolated systolic hypertension category. The cases were classified into the different stages as per the JNC-7 classification for hypertension. Known cases of hypertension, on treatment with a well controlled

blood pressure of <140/90 mm of hg were categorized under controlled hypertension.

Table - 4 shows that the mean serum uric acid levels were found to be 4.78 (2.32) mg/dl, 4.42 (1.38) mg/dl, 6.57 (1.55) mg/dl and 4.44 (1.44) mg/dl in controlled hypertension, stage 1 hypertension, stage 2 hypertension and isolated systolic hypertension respectively. Data analysis done by one way Anova test showed significant difference between stage 2 of hypertension with the stage 1 hypertensives, isolated systolic hypertensives and well controlled hypertensives with the p values of 0.001, 0.001 and 0.002 respectively. In the total of 80 hypertensives, 41 of them were on treatment and 39 of them were not on treatment and the mean serum uric acid value was 4.98 (1.76) mg/dl and 5.67 (1.97) respectively. Cases were classified as newly detected hypertensives if they were detected to have hypertension as per the standard blood pressure measurements for the first time or during the previous 14 days and not on any form of treatment. The mean systolic blood pressures recorded were 127.13 mm of hg, 149.25 mm of hg, 164.66 mm of hg and 160 mm of hg in the controlled hypertensive group, stage 1 hypertension, stage 2 hypertension and the isolated systolic hypertensive group respectively (**Figure – 2, 4**).

Table – 3: shows number of cases in different stages of hypertension with sex wise distribution.

Stage	Males	Females	Total
Controlled hypertension	10	4	14
Stage 1	17	9	26
Stage 2	25	6	31
Isolated systolic hypertension	6	3	9

Table – 4: shows mean uric acid levels in mg/dl of cases in different stages of hypertension.

Stage	Males (SD)	Females (SD)	Total (SD)
Controlled hypertension	5.18 (3.80)	3.80 (1.32)	4.78 (2.32)
Stage 1	4.32 (1.47)	4.60 (1.26)	4.42 (1.38)
Stage 2	6.75 (1.57)	5.83 (1.30)	6.57 (1.55)
Isolated systolic hypertension	4.12 (1.24)	5.10 (0.62)	4.44 (1.14)

Figure – 2: shows mean systolic blood pressure.

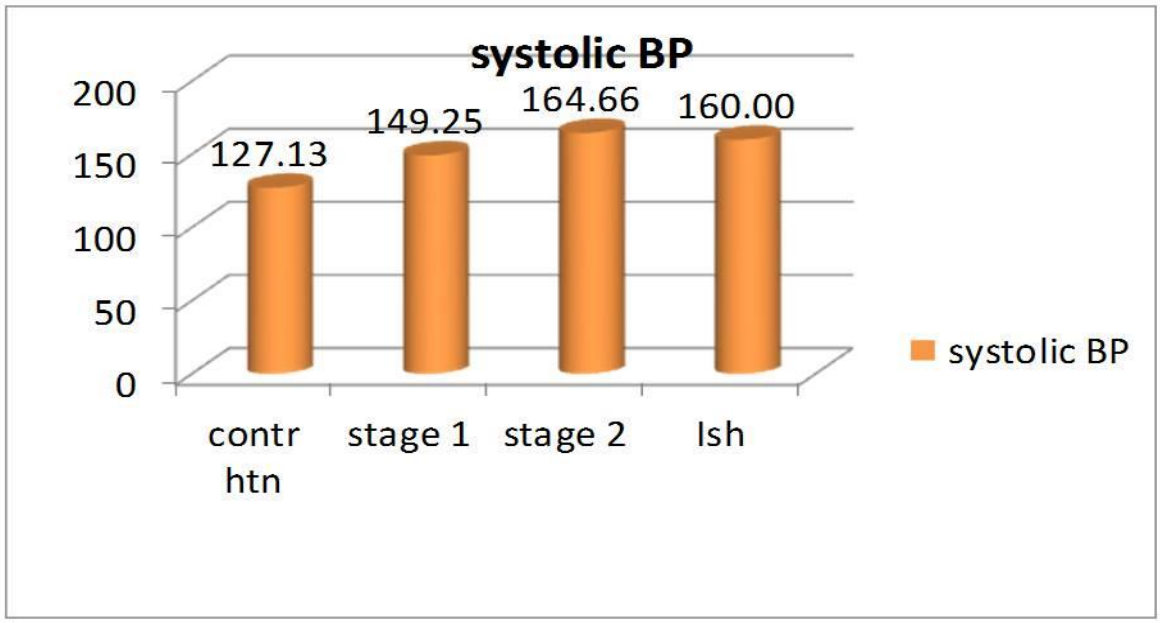


Figure – 3: shows mean diastolic BP.

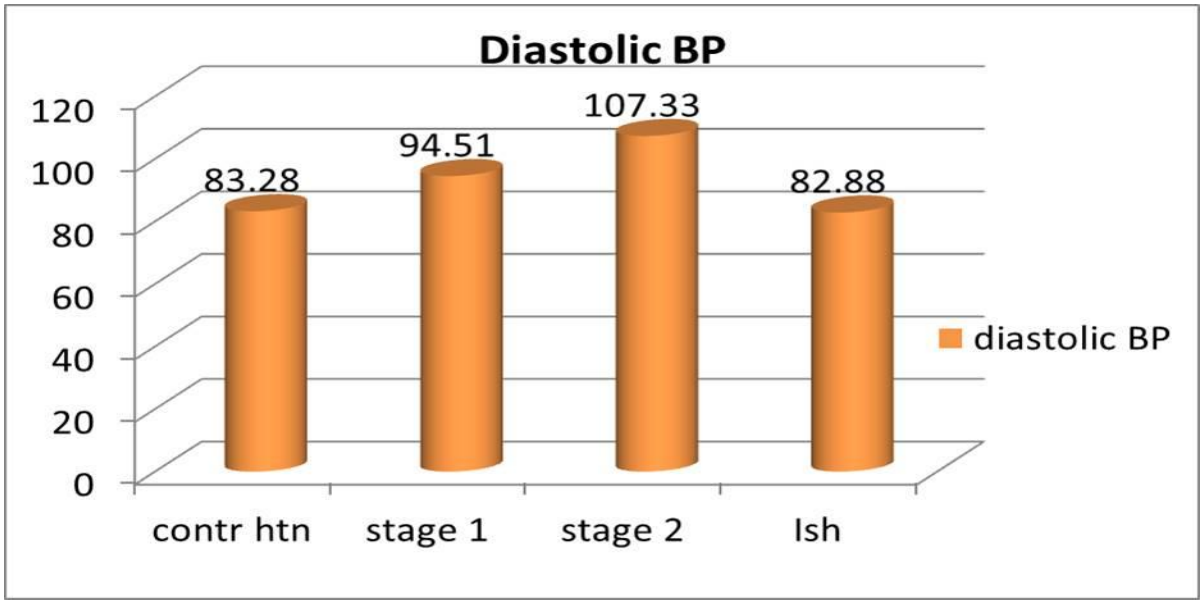
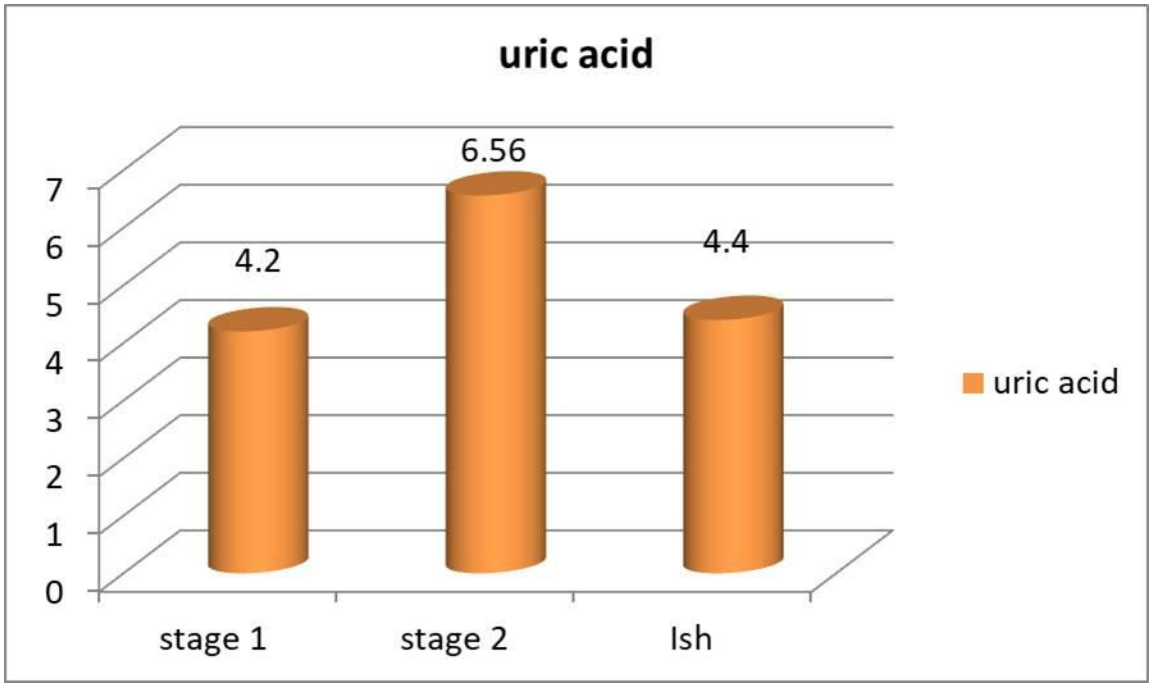


Table – 5: shows newly diagnosed hypertensives.

	Stage 1 hypertension (SD)	**Stage 2 hypertension (SD)**	**Isolated systolic hypertension (SD)**
Total no.	13	22	4
Mean serum uric acid in mg/dl	4.20(1.37)	6.56(1.40)	4.40(1.40)

Figure – 4: shows the mean serum uric acid values of newly detected hypertensives in different stages of hypertension.



The mean diastolic blood pressures recorded were 83.28 mm of hg, 94.51 mm of hg, 107.33 mm of hg and 82.88 mm of hg in the controlled hypertensive group, stage 1 hypertension, stage 2 hypertension and the isolated systolic hypertensive group respectively (**Figure – 3**).

The age group in cases (hypertensives) ranges from 19 years to 82 years. In males it ranges from 19 years to 81 years and females it ranges from 32 years to 82 years. The age group in controls (non hypertensives) ranges from 20 years to 81 years. In males it ranges from 20 years to 81 years and females it ranges from 26 years to 78 years.

Table - 5 shows that the total number of newly detected hypertensives were 39 out of which 13 were diagnosed as stage 1 hypertension, 22 as stage 2 hypertension and 4 as isolated systolic hypertension. The mean of the serum uric acid was 4.20(1.37) mg/dl, 6.56(1.40) mg/dl and 4.40(1.40) in stage 1 hypertension, stage 2 hypertension and isolated systolic hypertension respectively, in newly diagnosed hypertensives.

Discussion

Elevated serum uric acid levels have been associated with an increased risk for cardiovascular disease. The potential mechanisms by which serum uric acid may directly affect cardiovascular risk include enhanced platelet aggregation and inflammatory activation of the endothelium [3]. In few studies, the association of serum uric acid with cardiovascular disease was uncertain after multivariate adjustment as in the Framingham Heart Study [4] and the ARIC study , but in others such as the study done by verdecchia, et al. [5] the association remained certain and significant. Because elevated serum uric acid is correlated with several risk factors including renal dysfunction, hypertension, insulin resistance, hyper-homocystenemia and hyperlipidemia, it is debated whether serum uric acid is an independent cardiovascular risk factor. In the present study the mean serum uric acid in the hypertensive group was 5.49 (1.86) mg/dl in males and 4.86 (1.47) mg/dl in females. On the other hand the mean serum uric acid level in the control group was 4.02 (1.09) mg/dl in males and 3.32 (1.196) mg/dl in females. Data analysis by T-test, done to compare the mean serum uric acid values in hypertensives with that of non hypertensives was proven to be significant with a p value of <0.001. Data analysis by one way Anova test was done to compare the mean serum uric acid and their significance between the different stages of hypertension and showed the following results. Non hypertensives and stage 1 hypertension p value of 0.337. Non-hypertensives and stage 2 hypertension p value of <0.001. Non hypertensives and controlled hypertension p value of 0.116. Non hypertensives and isolated systolic hypertension p value of 0.664. Though the difference in serum uric acid levels were found to be more in other stages of hypertension as compared to the non hypertensives, statistical significance was found only in stage 2 hypertensives when compared to non hypertensives. There was also significant difference noted between stage 2 of hypertension with the stage 1 hypertensives, isolated systolic hypertensives and well controlled hypertensives with the p values of 0.001, 0.001 and 0.002 respectively. There is a considerable difference in the mean serum uric acid levels between stages 1, 2 and isolated systolic hypertension in the newly detected hypertensives but it is not of a linear correlation. The mean serum uric acid levels in the hypertensives on treatment was 4.90 (1.97) mg/dl and those not on treatment was 5.67 (1.76) mg/dl with a p-value of 0.514. Hence it appears that treatment of hypertension does not cause significant difference in the serum uric acid levels. In the PIUMA study involving 1720 subjects who were followed up for 12 years Verdechchia, et al. has reported that in untreated subjects with essential hypertension, raised uric acid is a powerful risk marker for subsequent cardiovascular disease and all-cause mortality [5]. Abdallah Jeraiah, et al. In the study involving 49 known hypertensive (31 males and 18 females) and 16 healthy controls (without hypertension) reported serum uric acid levels from patients taken from various hospitals with hypertension increased significantly when compared with controls ($p < 0.001$). Male and female hypertensive patients had showed significant increase in serum uric acid levels when compared with controls ($p < 0.001$) [6]. Selby, et al. conducted a nested case-control

study of 1,031 cases of essential hypertension and 1,031 persistently normotensive controls from the Kaiser Permanente Multiphasic Health Checkup cohort in Northern California adjusting for the risk factors, forced vital capacity (p less than 0.001), serum uric acid (p = 0.003), serum cholesterol (p = 0.012), and heart rate (p = 0.014) remained independently predictive for essential hypertension. Uric acid remained positively related to risk (odds ratio, fifth vs. first quintile = 2.19, 95% Cl 1.20-3.98). Both forced vital capacity and serum uric acid are closely linked to development of hypertension and may be markers of susceptibility or intermediate steps in pathways leading to hypertension [7]. Fessel, et al. observed an elevation of systolic blood pressure in hyperuricemic patients but no elevation of diastolic blood pressure could be observed [8]. Myers, et al. reported some elevation of serum uric acid level in accordance with the increased blood pressure, but it was not a definite correlation [9]. Zainab Abdul Razak, et al. in their study in Iraq featuring 20 cases and 15 controls had a mean serum uric acid value of 8.03(3.50) mg/dl in comparison to 4.32(1.07) mg/dl with a significant p value of <0.05. The study showed that the serum levels of uric acid, CRP and total cholesterol were significantly higher in patients with hypertension than in healthy controls [10]. It certainly is possible that uric acid may be an earlier and more sensitive maker of decreased renal blood flow than serum creatinine. It has been recently suggested that since uric acid may play a role in the formation of free radicals and oxidative stress, the increased risk of hypertension in subjects with raised serum uric acid levels might be associated with this increased generation of free radicals. Several observations support this concept of free radical mediated inhibition of endothelium dependent vasodilation. An antioxidant deficiency in diet which produces hyperuricemia, contributes to the etiology of hypertension, and the antioxidant drugs also show a blood pressure lowering effect in both diabetic and hypertensive patients [11]. Three possible conclusions can be drawn from the association of hypertension with raised serum uric acid levels. Hypertension may arise as a result of hyperuricemia, hypertension can cause hyperuricemia and the duration and severity of hypertension is related directly to the serum uric acid levels [12]. In gouty patients without advanced tophi, however renal failure and hypertension are rare. In a group of 80 patient's attending the Hammersmith hospital gout clinic only 2 were hypertensive. In a study of gouty patients of Northern India by Kumar, et al. they found that only one out of 30 patients had hypertension [13]. Fessel, et al. showed no appreciable loss of renal function in 112 patients with gout as compared to normal subjects followed up for 12 years [8]. In a study by Lawrence E Ramsay there was no evidence that hyperuricemia had a deleterious effect on renal function [14]. Canon, et al. considered that an impairment of renal function will raise the serum uric acid levels more commonly than an increased serum uric acid will cause renal damage [15]. Hence it is unlikely that hypertension arises as a result of raised serum uric acid levels, but the possibility that uric acid which plays a role in the formation of free radicals and oxidative stress, the increased risk of hypertension in subjects with raised serum uric acid levels might be associated with this increased generation of free radicals. Hence the fact that raised serum uric acid levels can lead to Hypertension cannot be entirely ruled out. As to the possibility that Hypertension can cause hyperuricemia, it is thought that hyperuricemia can result from either overproduction of uric acid or from under excretion of uric acid. Overproduction of uric acid can be measured by the rate of incorporation of acid precursors such as Glycine labeled N 15, into the uric acid pool. Such a study carried out in 4 hypertensive patients with raised serum uric acid levels did not show any overproduction of uric acid. In the study of Breckenridge [1] excretion of uric acid and uric acid clearance were lower in all hypertensive patients than in the normal group. When the uric acid clearance was expressed per 100ml of glomerular filtrate, there was no significant difference between normal subjects and hypertensive patients who had normal serum uric acid levels, but the difference between those

2 groups and the hyperuricemic hypertensives was significant and they suggested a renal tubular abnormality in the handling of uric acid, the nature of the abnormality which was not clear. Later Messerli, et al. showed that hyperuricemia in hypertensive is due to early renal vascular involvement, namely nephrosclerosis [11]. Serum uric acid rises because of impaired renal tubular function, which is the main site of regulation of serum uric acid due to nephrosclerosis. Tykarski in his study showed that serum uric acid levels in hypertensives are due to impaired tubular secretion of urate [16]. In the present study incidence and severity of elevated serum uric acid levels between cases and controls correlated significantly with the severity of hypertension. This correlated with both the Kinsey [17] and Breckenridge [1] studies, but according to Cannon, et al. [15] severity of hypertension had no relation to serum uric acid levels. Our study agrees with the study of Tykarski, et al. in that there is a positive correlation between serum uric acid and severity of hypertension [16] as per the stages but it is not of a linear correlation. Breckenridge in his study showed an increasing incidence of hyperuricemia as the diastolic BP increased in his study, but there was no tendency for hyperuricemia to occur, only with patients with more severe hypertension [1]. The PIUMA study demonstrates a strong independent association between serum uric acid levels and CV risk in initially untreated and asymptomatic adult subjects with essential hypertension, but it is unable to answer the question of whether serum uric acid exerts direct toxic effects. As extensively reviewed by Puig and Ruilope [18], both uric acid and superoxide radicals are produced for the effect of xanthine oxidase in the late phase of purine metabolism. Superoxide radicals, which may cause tissue and vascular damage, are increased in subjects with essential hypertension. It would be important to clarify whether such increase is due, at least in part, to enhanced xanthine oxidase activity and whether inhibition of this enzyme by allopurinol may reduce CV risk. In our study it was found that there is definite relation in serum uric acid levels between hypertensive patients and normotensive patients and there is a directly proportional relation in the levels of serum uric acid in relation to the severity of hypertension, though it is not of a linear correlation. Also it was found that there was no significant difference in the levels of serum uric acid in hypertensives on treatment as compared to those not on treatment. Hence the possibility of serum uric acid acting by the production of free radicals and causing oxidative stress leading to hypertension and whether the duration and severity of hypertension lead to renal dysfunction in the form of nephrosclerosis leading to higher levels of serum uric acid has to be considered as various other studies have also shown to have a positive relation in the serum uric acid levels and hypertension.

Conclusion

Thus based on the study carried out we can conclude that serum uric acid is significantly elevated in hypertensives as compared to normotensive individuals. Serum uric acid can be used probably as an early biochemical marker to determine the severity of hypertension as stage 2 hypertensives had more elevation in serum uric acid levels as compared to other hypertensives. The uric acid levels did not differ significantly between hypertensives with and without treatment. There is a considerable difference in the mean serum uric acid levels between stages 1, 2 and isolated systolic hypertension in the newly detected hypertensives but it is not of a linear correlation. Thus serum uric acid estimation can be used for aiding in the diagnosis of essential hypertension as well as in assessment of the severity.

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